

9th Gynaecological Cancer Symposium
Derby Deltacentre 26th February 2016

Ovarian Cancer Screening Trials

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Disclosure

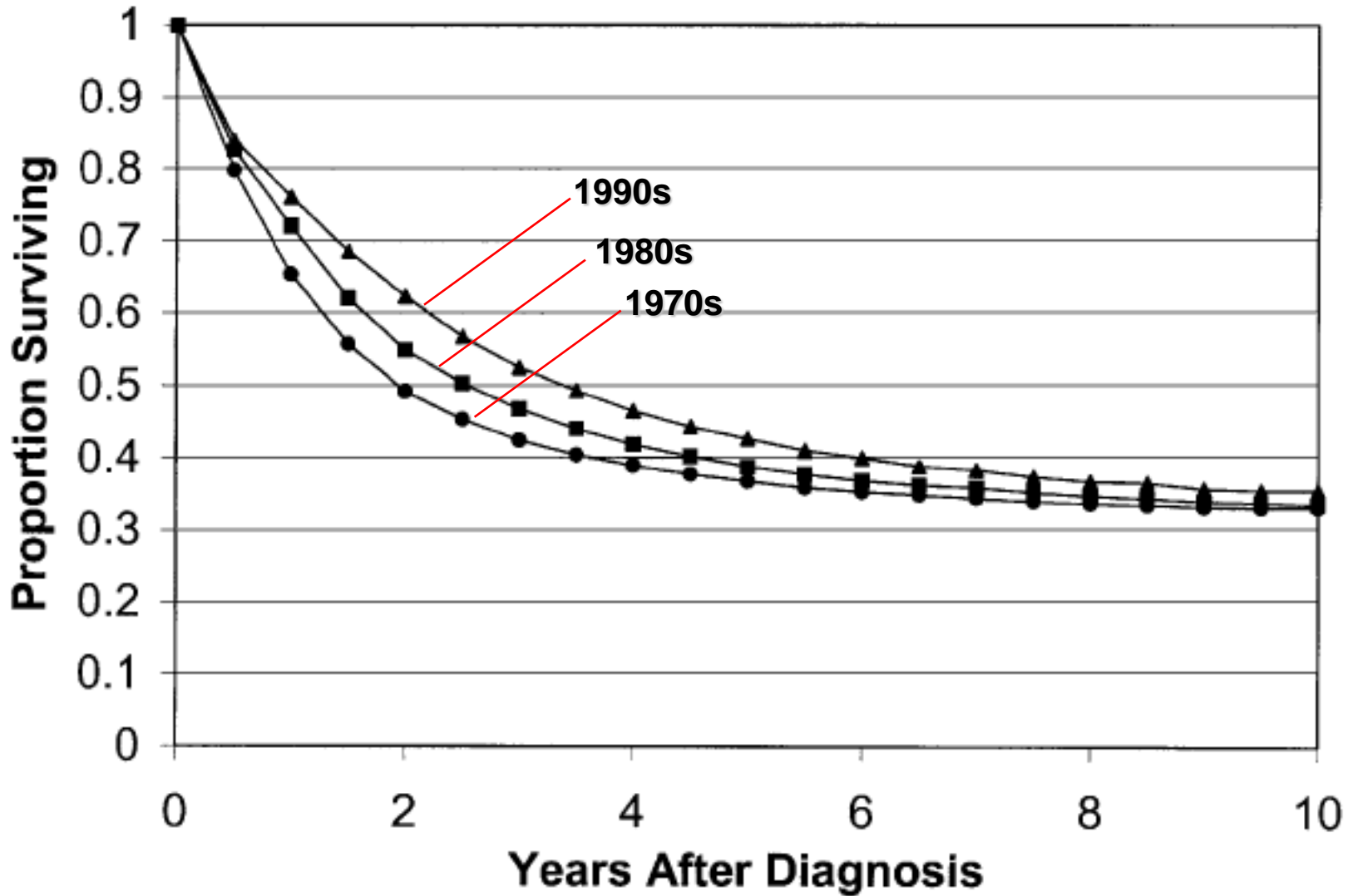
- **Honoraria from Fujirebio and Roche**
- **Astra Zeneca expert panel**
- **Consultancy with Myriad Genetics**
- **Consultancy with Abcodia**

Ovarian Cancer Screening Trials:

- **Why screen?**
- **General population screening**
- **Rational use of screening in 2016**

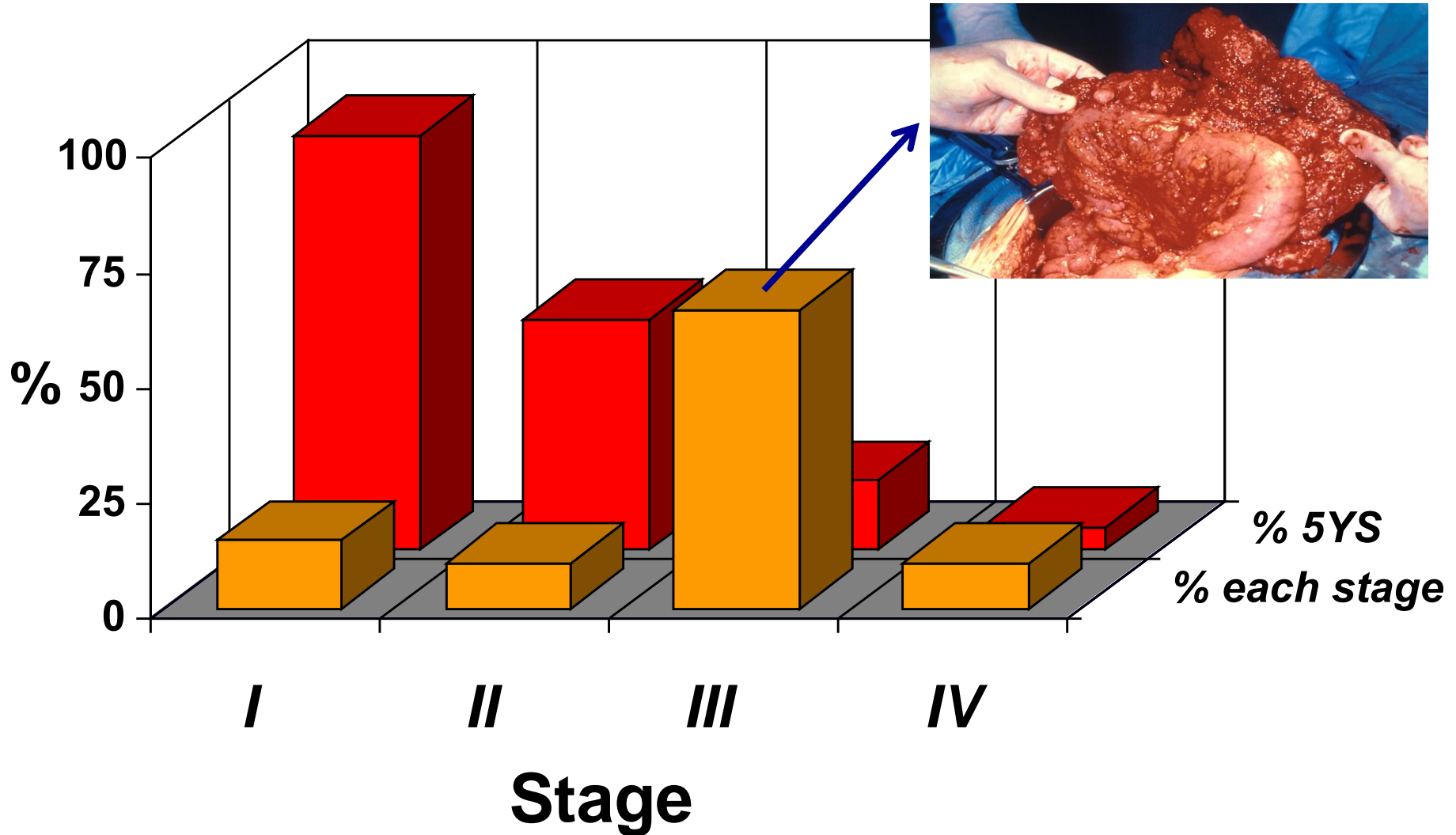
Ovarian Cancer Screening Trials

- **Why screen?**
- **General population screening**
- **Rational use of screening in 2016**



32,840 women with epithelial ovarian cancer

Ovarian cancer stage vs. survival



Ovarian Cancer Screening Trials

- Why screen?
- **General population screening**
- Rational use of screening in 2016

Who is included in general population screening?

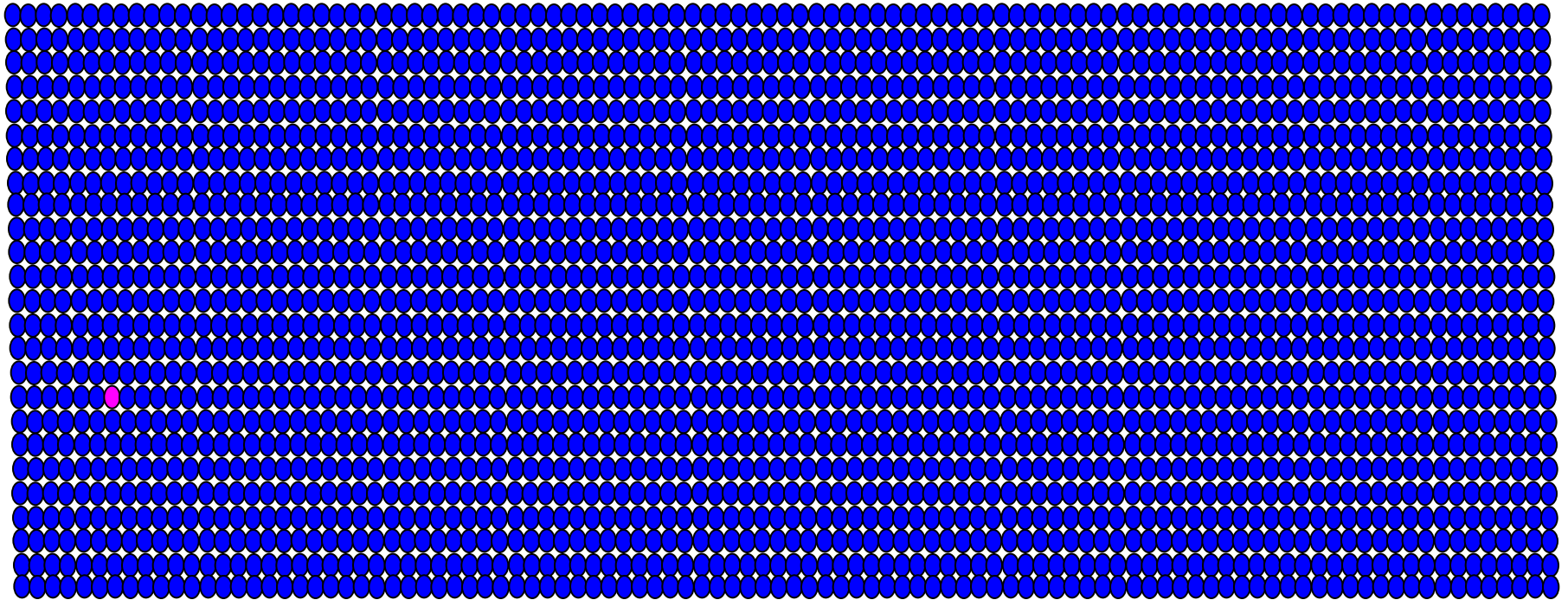
- Post-menopausal women
- Women without a family history suggestive of inherited predisposition to ovarian cancer (e.g. *BRCA1*)

Not symptomatic women!

Requirements of ovarian cancer screening test

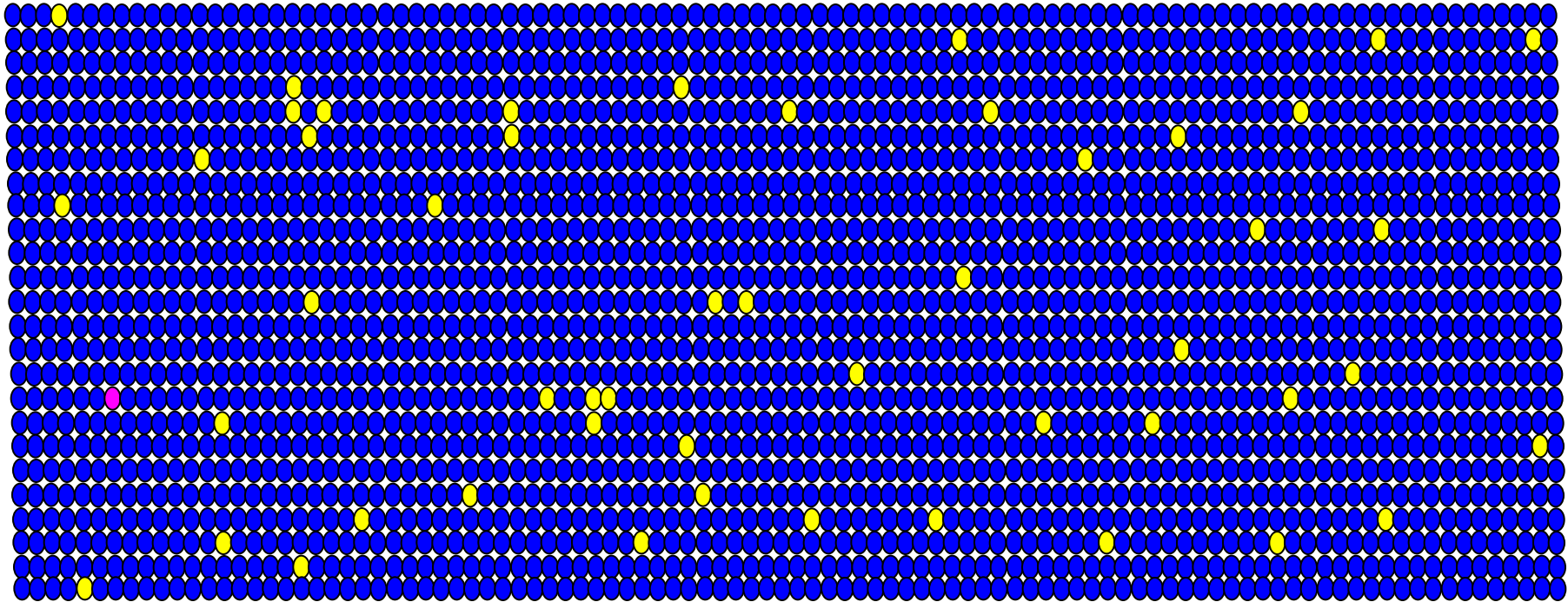
- **High sensitivity - for early stage disease**
- **High specificity - 99.6% in general population results in
10:1 false positive rate**
- **Feasible**
- **Acceptable**
- **Cost effective**

The challenge of ovarian cancer screening (1)



**1 in 2,500 postmenopausal women per year
develop ovarian cancer**

The challenge of ovarian cancer screening (2)

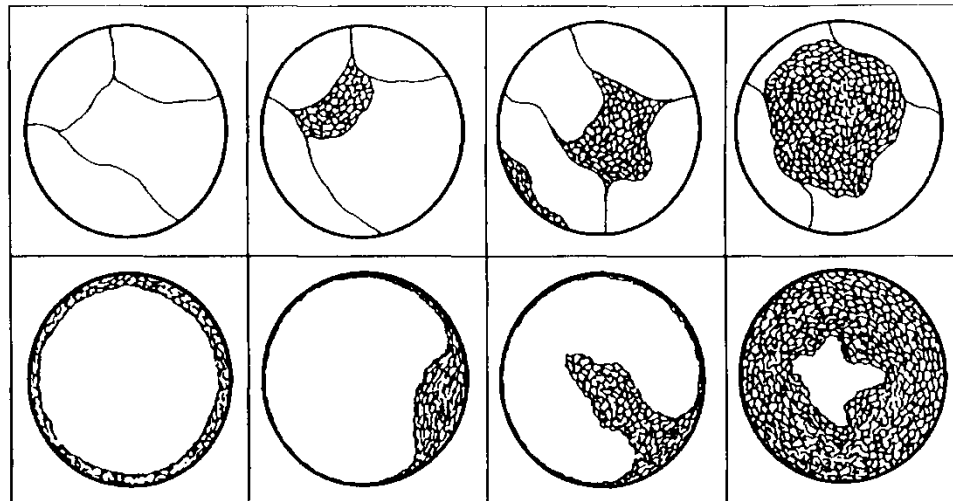


Transabdominal Ultrasound or CA125 using cutpoint:
2% False Positive Rate means 50 unnecessary operations
To identify one patient with ovarian cancer

Refining Ultrasound Screening

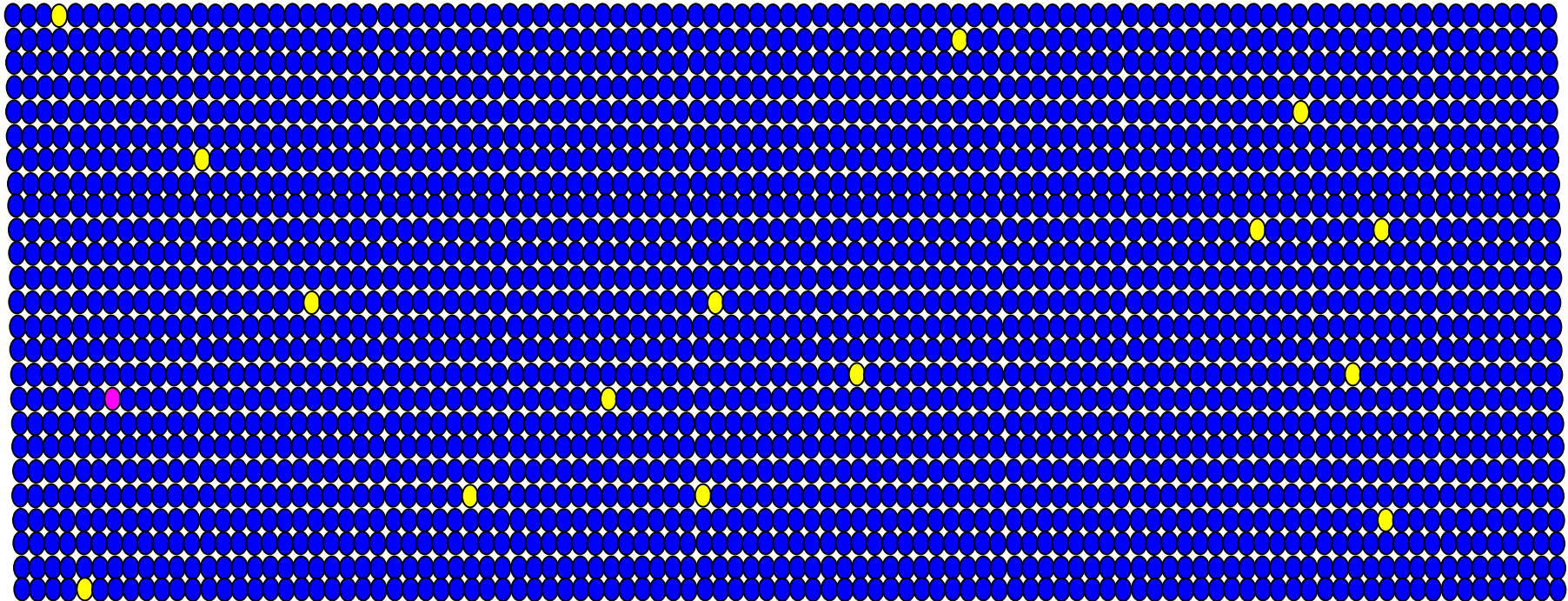
- Transvaginal scanning
- Sophisticated machines with higher resolution
- Serial monitoring of abnormalities
- Development of morphology based scoring systems:

Septa structure



Wall structure

Refining ultrasound screening (2)

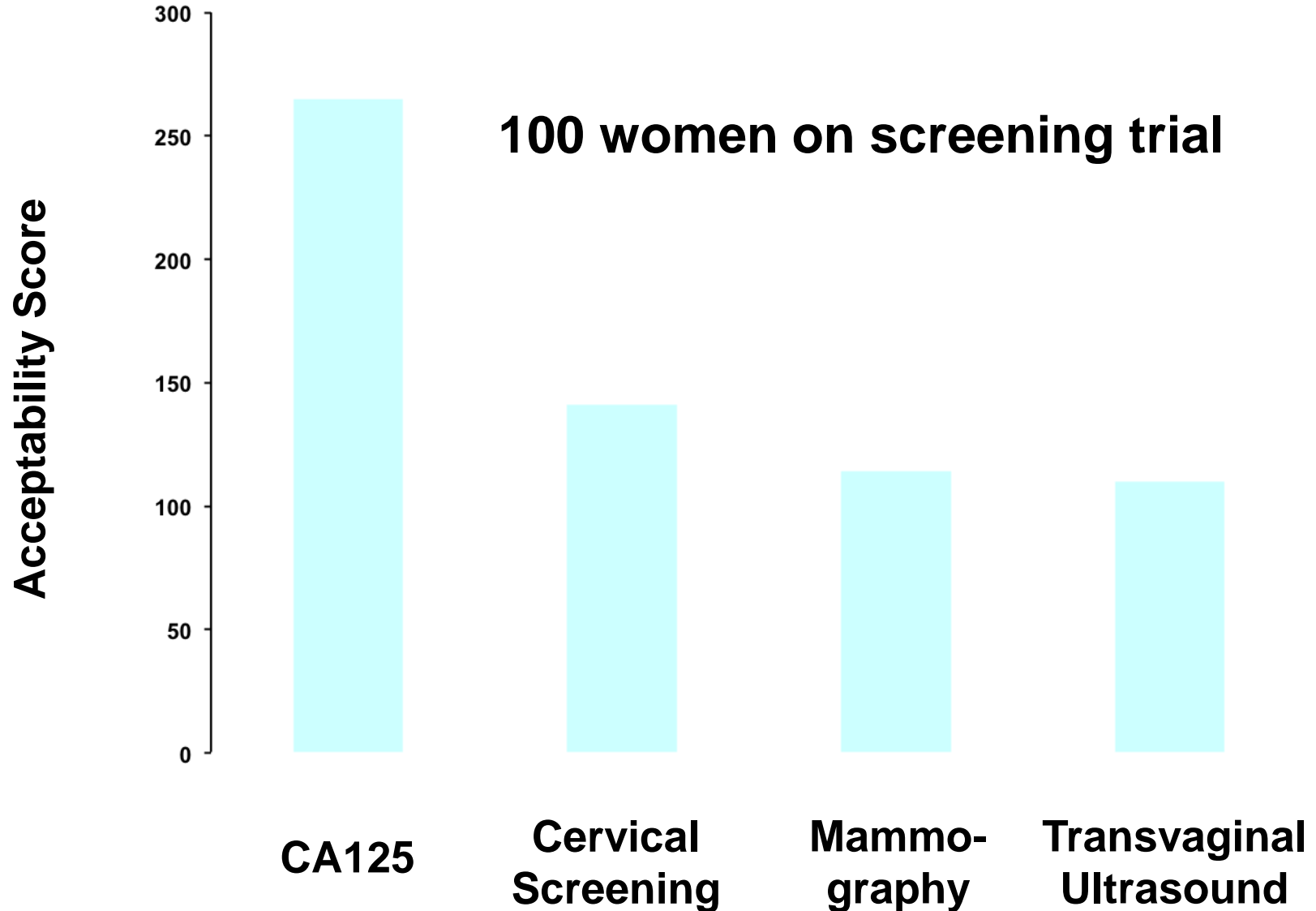


15 unnecessary operations to identify one patient with ovarian cancer

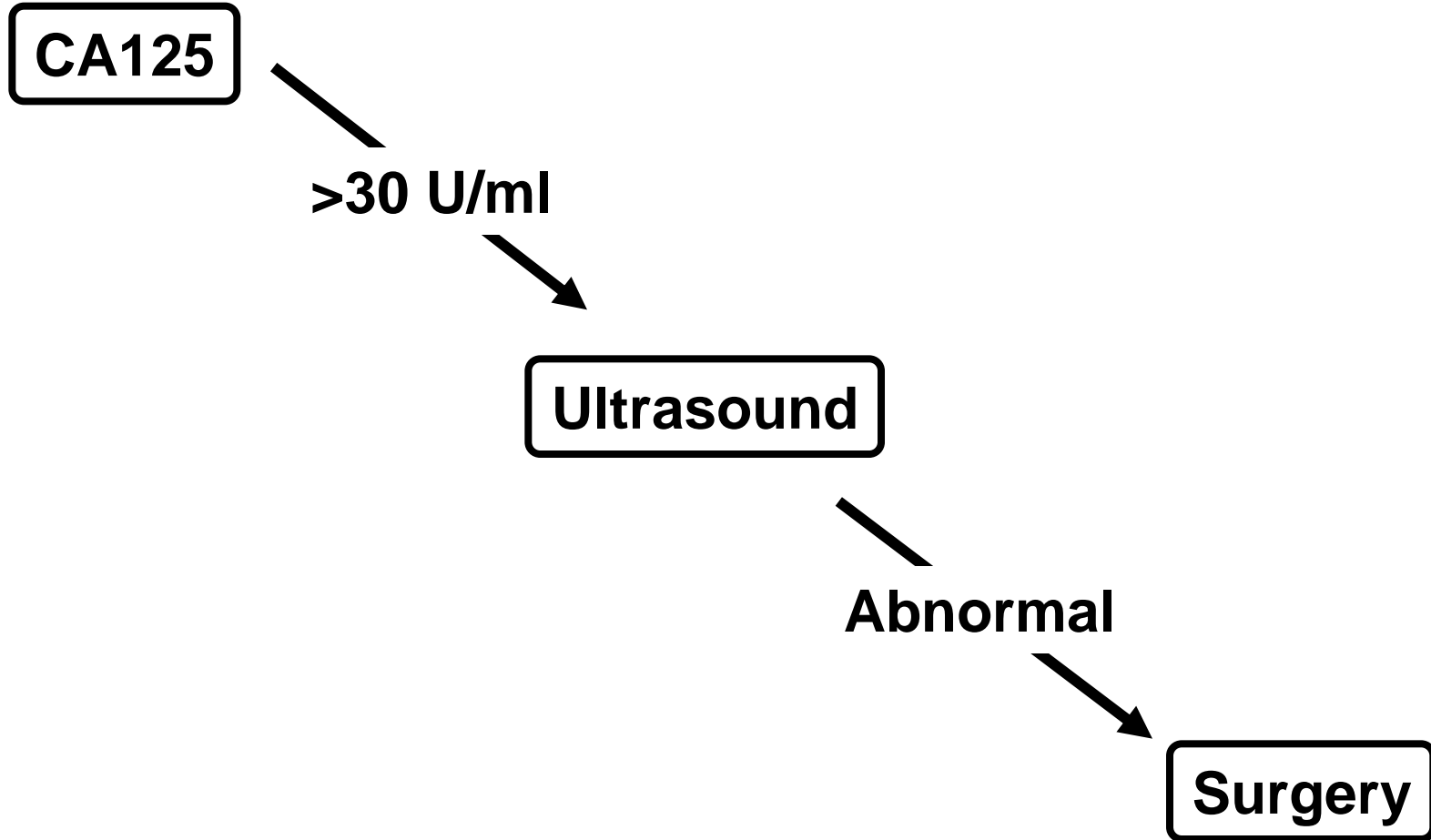
Advantages of screening with CA125

- **Sampling is quick, simple and can be performed anywhere**
- **Tests can be performed in one central laboratory**
- **Results are objective and reproducible**
- **Cost per test is relatively low**

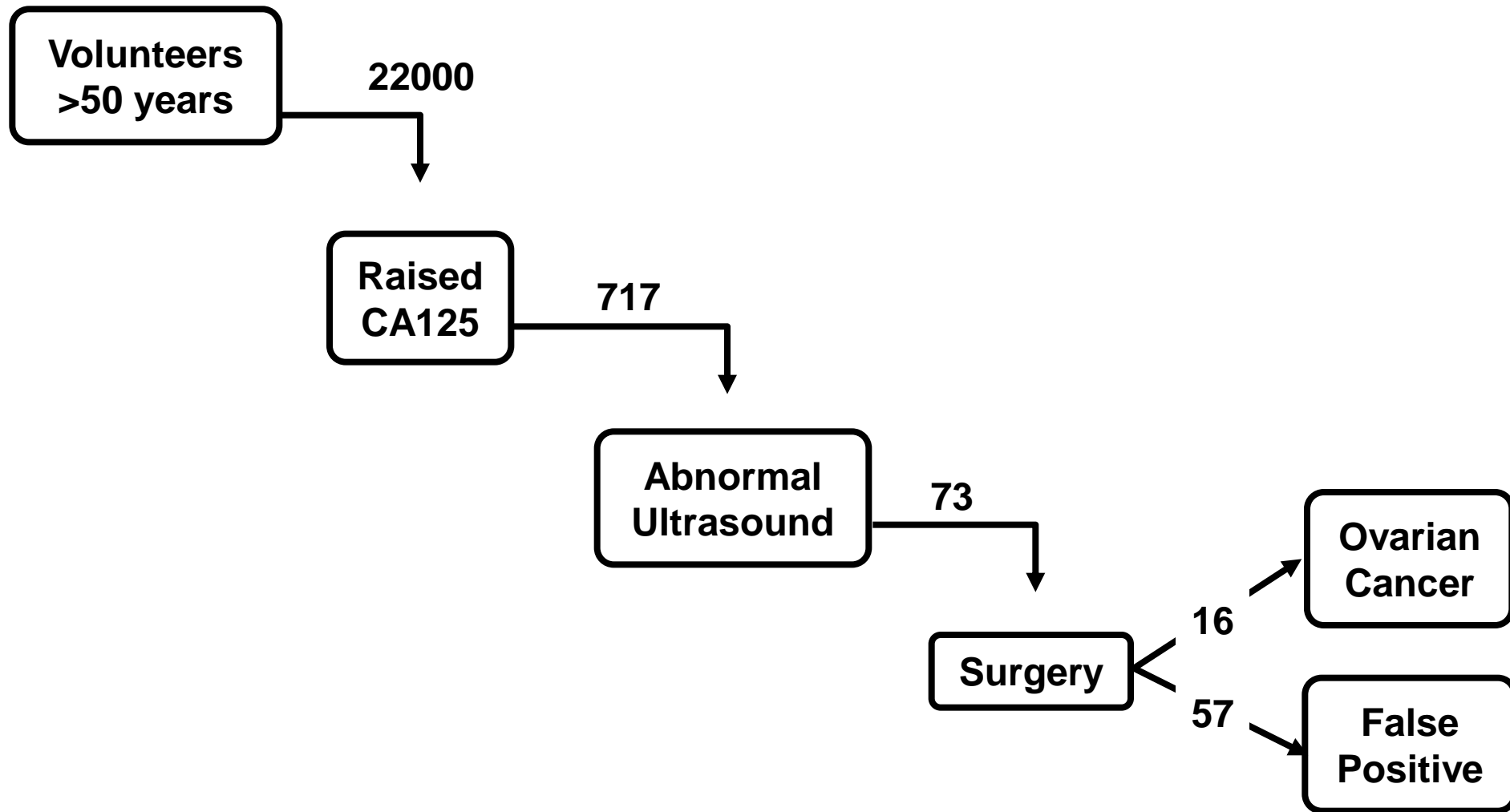
Is screening acceptable?



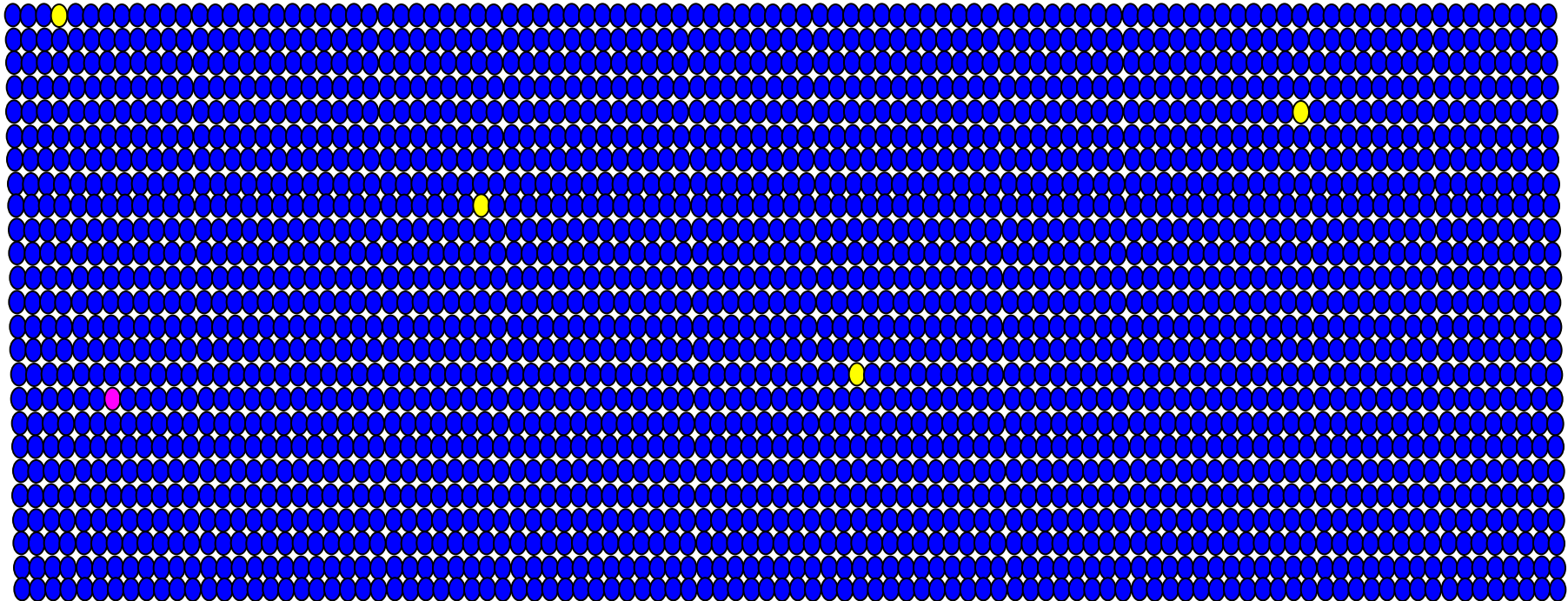
Multimodal Screening



Multimodal screening has a low false positive rate



Multimodal screening has a low false-positive rate



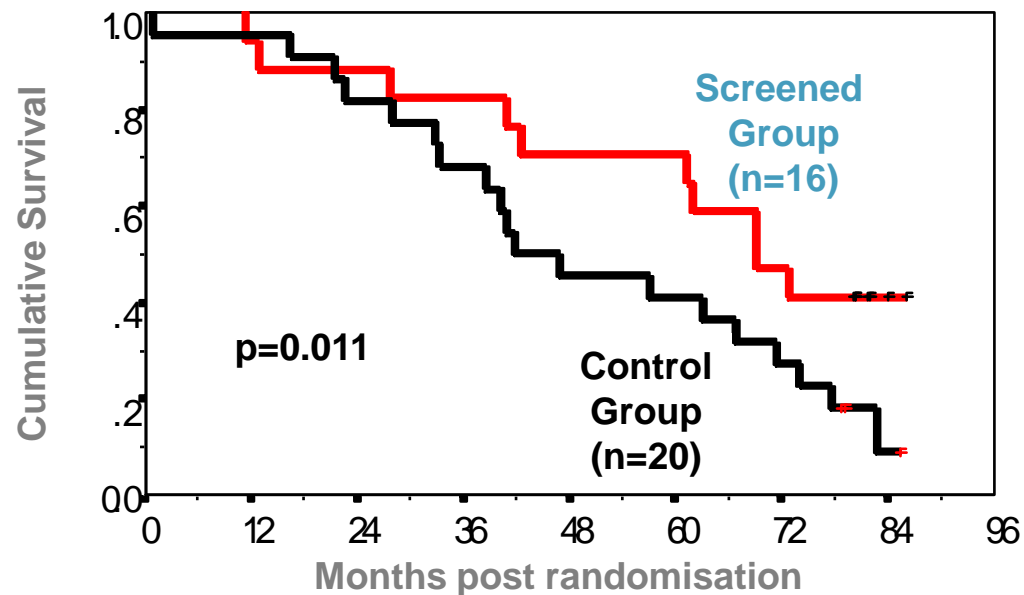
5 operations to identify one patient with ovarian cancer

Screening for ovarian cancer: a pilot randomised controlled trial

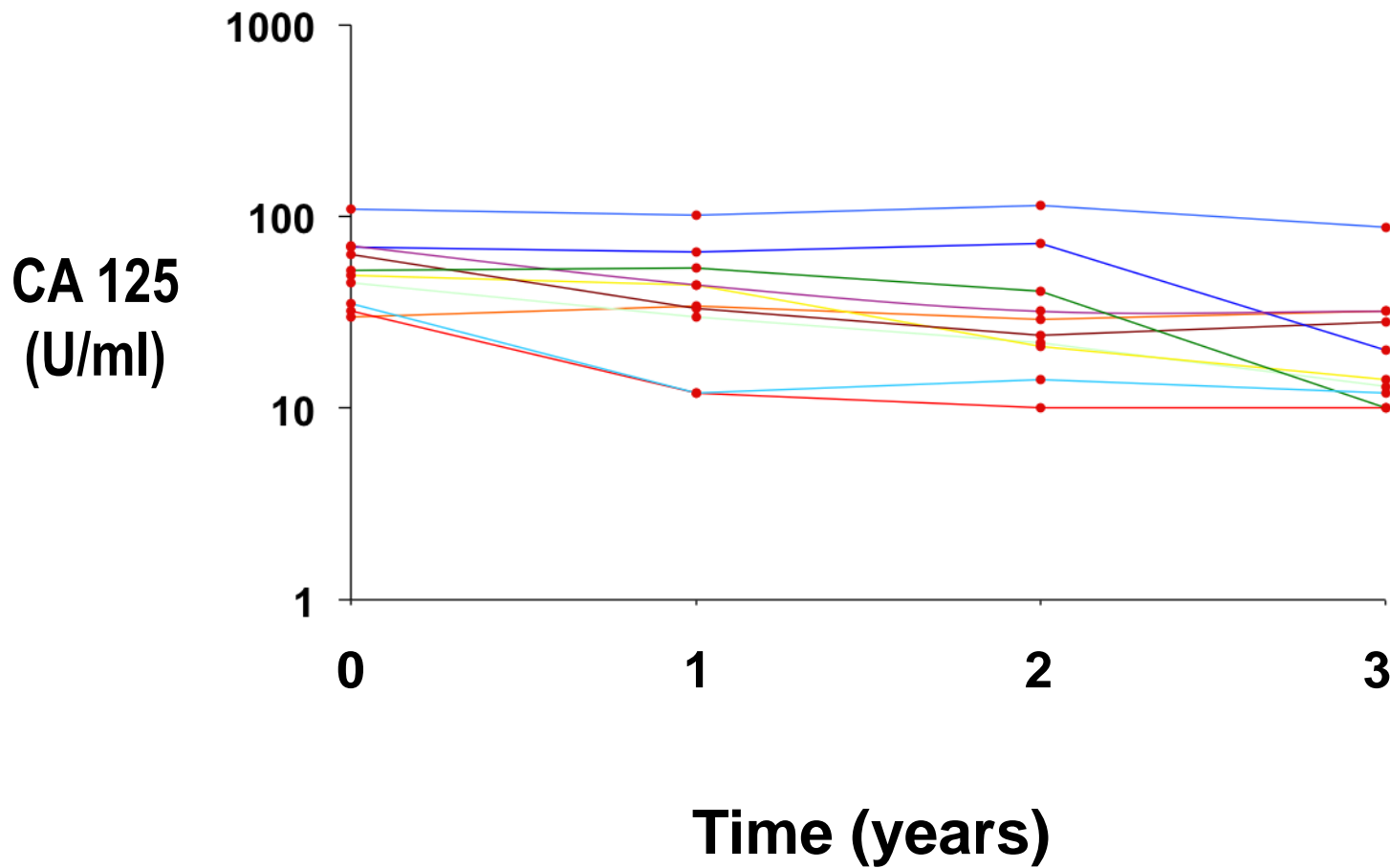
Ian J Jacobs, Steven J Skates, Nicola MacDonald, Usha Menon, Adam N Rosenthal, Ann Prys Davies, Robert Woolas, Arjun R Jeyarajah, Karen Sibley, David G Lowe, David H Oram

THE LANCET • Vol 353 • April 10, 1999

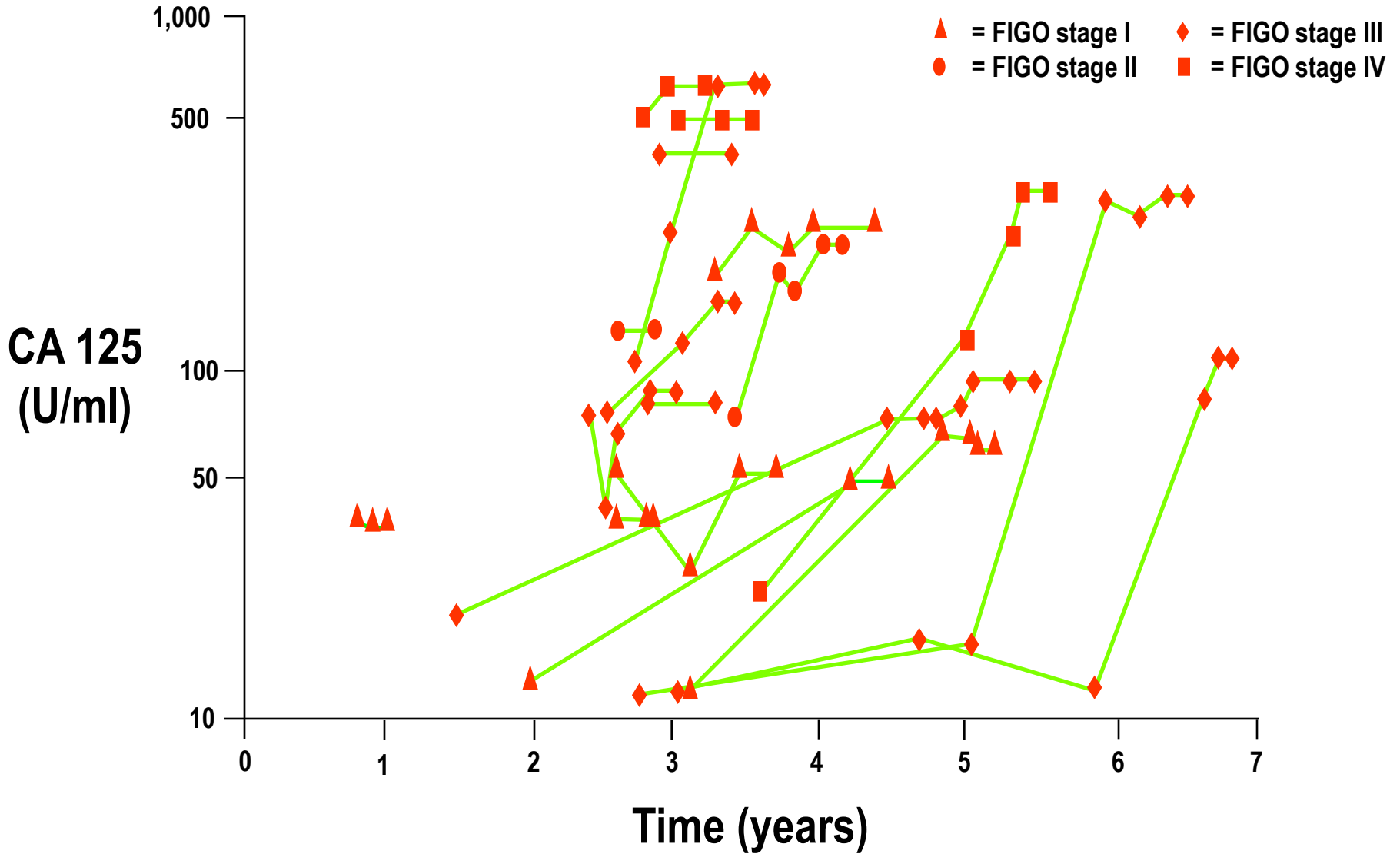
Median Survival 73mths versus 42mths



Risk of Ovarian Cancer Algorithm ROCA (1)



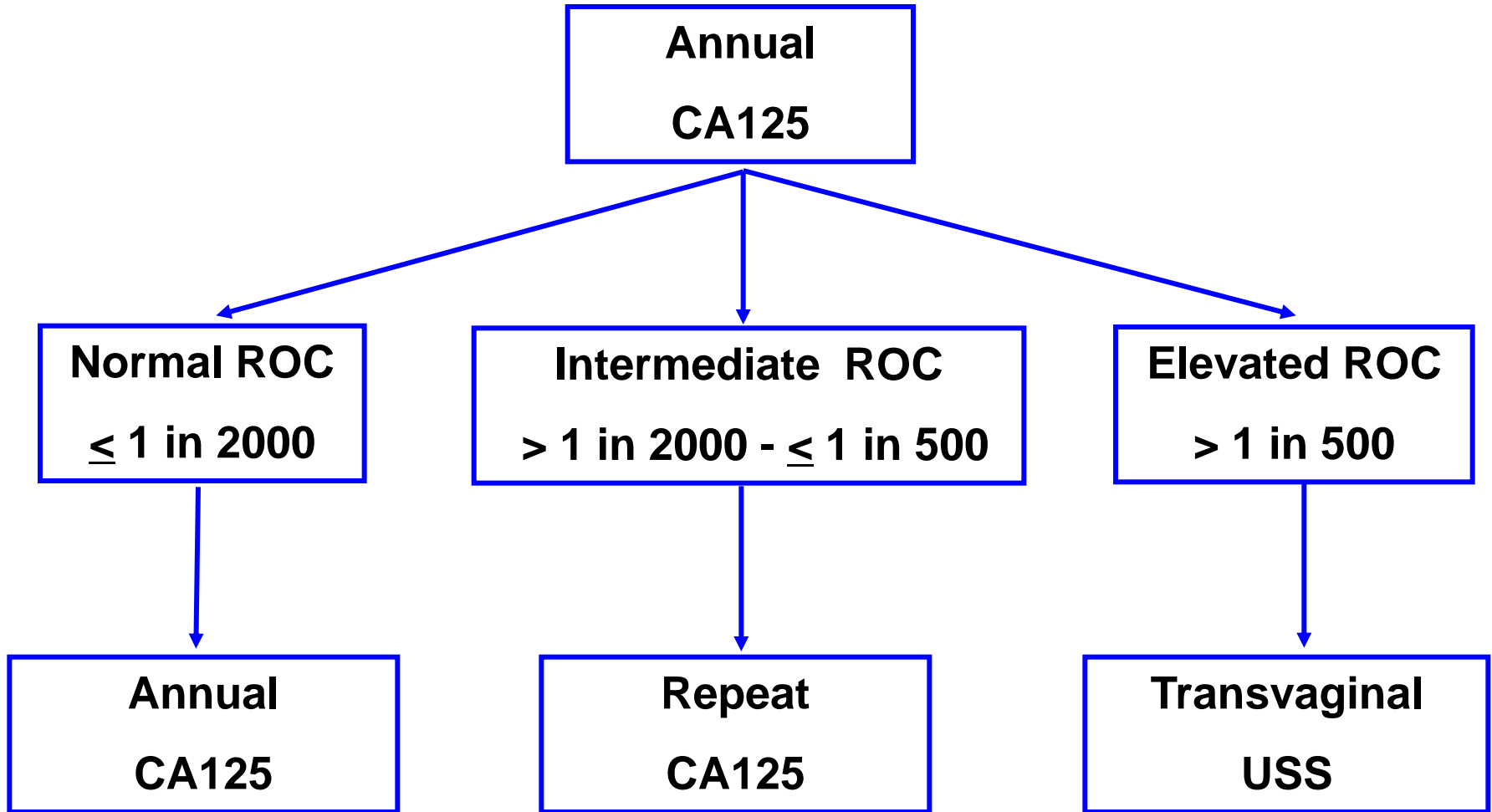
ROCA (2)



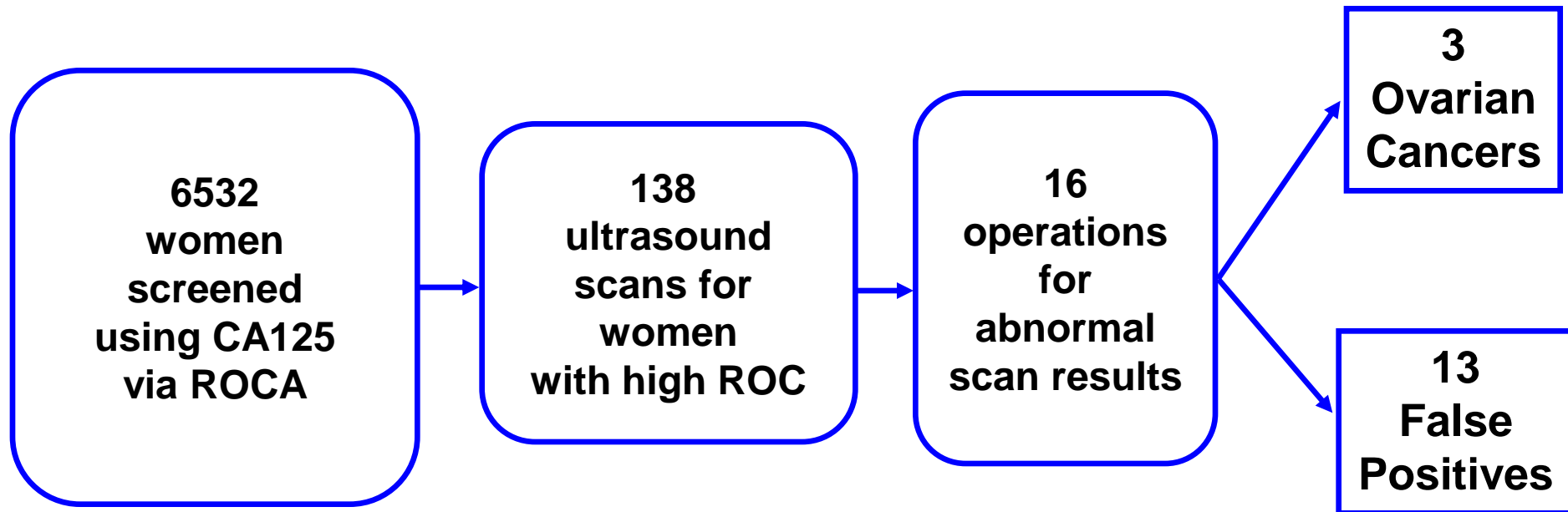
ROCA

- **Computerised algorithm which compares each individual's CA125 profile to pattern in known cases of ovarian cancer and to healthy women**
- **The closer the CA125 profile to known cases of ovarian cancer, the greater the risk of ovarian cancer**
- **Produces individual's percentage risk of having ovarian cancer**

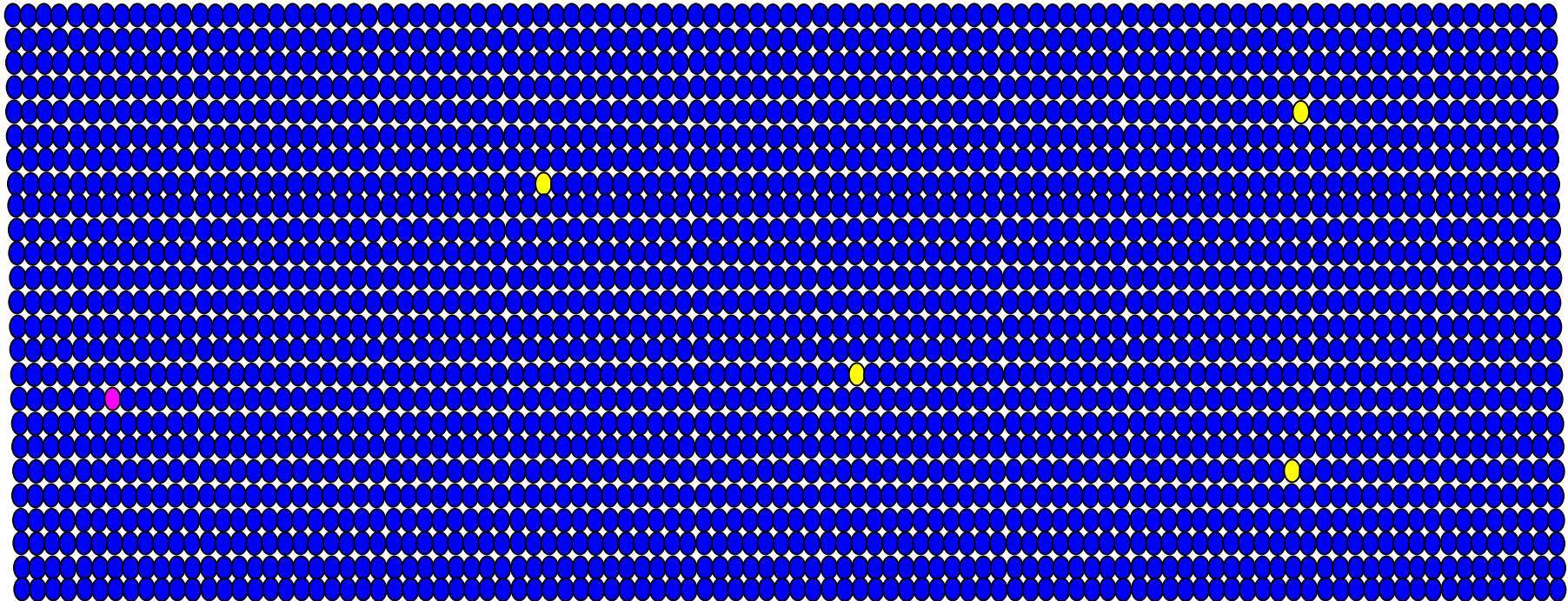
ROCA triage



Multimodal screening with ROCA & ultrasound

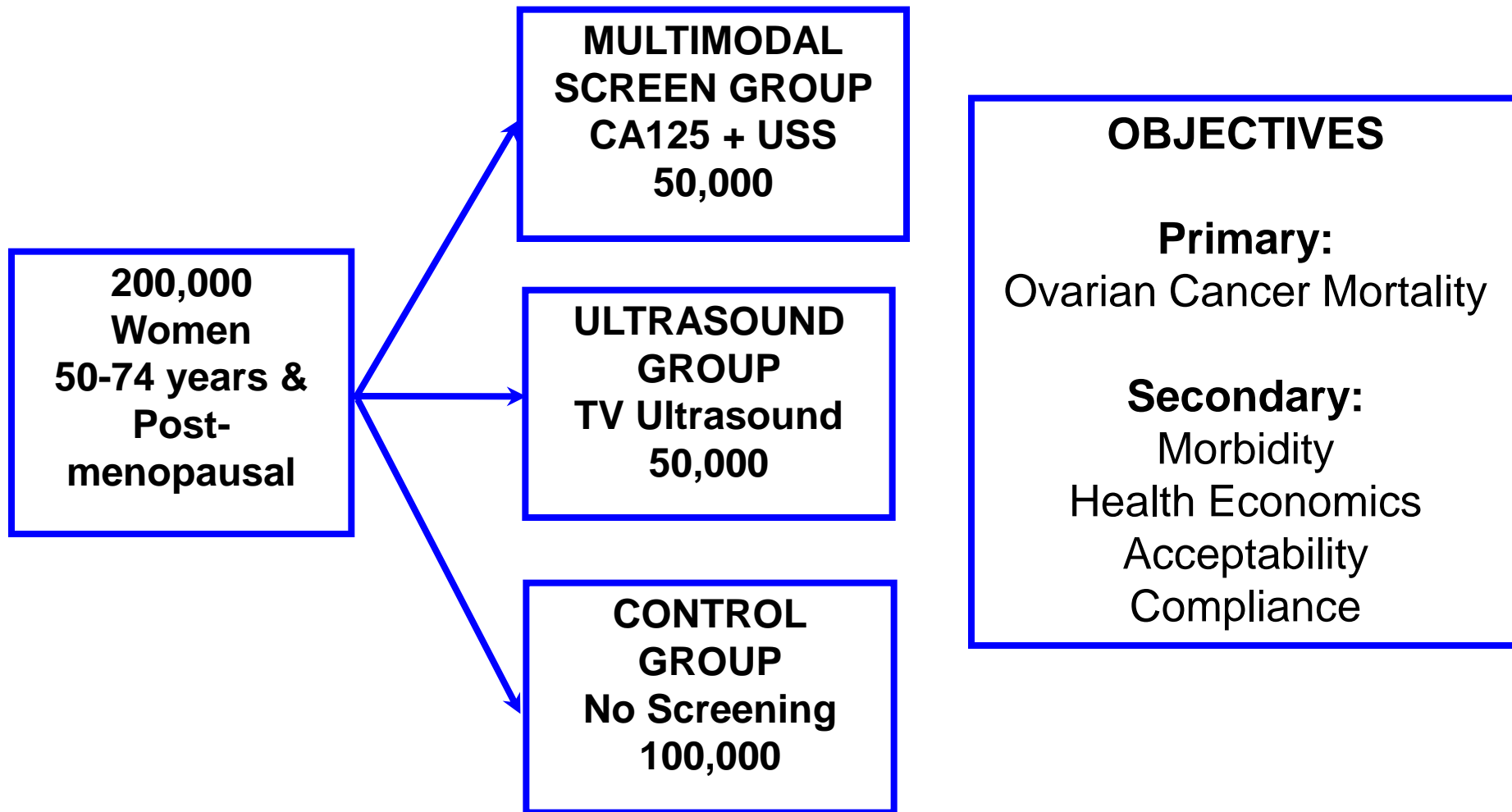


Multimodal screening with ROC algorithm followed by ultrasound



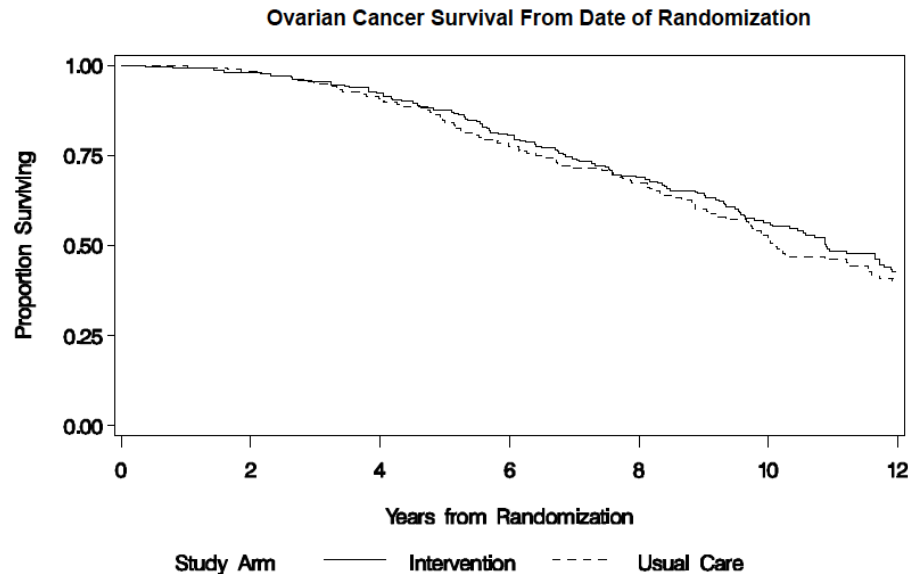
**5 operations to identify one patient with ovarian cancer
i.e. specificity maintained despite recalling women
with CA125 in normal range**

UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)



PLCO

39,000 annual TVS and CA125 screening vs. 39,000 usual care
 CA125 cut-off used, not ROCA



Number at Risk at Beginning of Year	Years Since Diagnosis													
	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Study Arm														
Intervention	212	210	207	201	195	183	168	153	140	125	95	69	47	16
Usual Care	176	176	173	167	160	148	135	123	114	98	72	54	35	15

PLCO

Problems with the study

- **40% cancers diagnosed after end of screening**
 - not clear what proportion diagnosed <1 yr of last screen, but no mortality benefit if analysis limited to 2 yr after end of screening
- **CA125 used cut-off, not ROCA**
 - improves specificity and sensitivity at values <35 iu/ml
- **Not protocol-driven management**
 - left to local physician to intervene at own discretion
 - median 2 month delay in acting on abnormal results
- **Why no stage shift?**
 - all other large studies show increased proportion early stage OC

UKCTOCS results so far

- **Prevalent screen = first screen**
i.e. detects cancers already present
- **Incidence screens = subsequent screens**
i.e. detect cancers which develop subsequently

UKCTOCS Prevalence Screen

50,078
women
screened
using CA125
via ROCA

97
operations

Sensitivity 89.4%
Specificity 99.8%

42
Ovarian
Cancers

55
False
Positives

48% Stage I or II

45
Ovarian
Cancers

48,227
women
screened
using ultrasound

845
operations

Sensitivity 84.9%
Specificity 98.2%

800
False
Positives

UKCTOCS Incidence Screening

46,237
women
screened
using CA125
via ROCA

640
operations

Sensitivity 85.8%
Specificity 99.8%

133
Ovarian
Cancers

441
False
Positives
+ 45 other cancers

PPV 21%

**5 operations for each case of OC
detected**

41% Stage I or II

82% type 2 OC (mainly HG serous)

ROCA outperforms CA125 cut-offs for
ovarian cancer screening

**ROCA doubles the number of cancers detected compared to a single
CA125 cut-off**

Menon et al, *J Clin Oncol* 2015

**Re-analysis of PLCO data using ROCA or another longitudinal model
could have picked up 1/3 of cancers sooner**

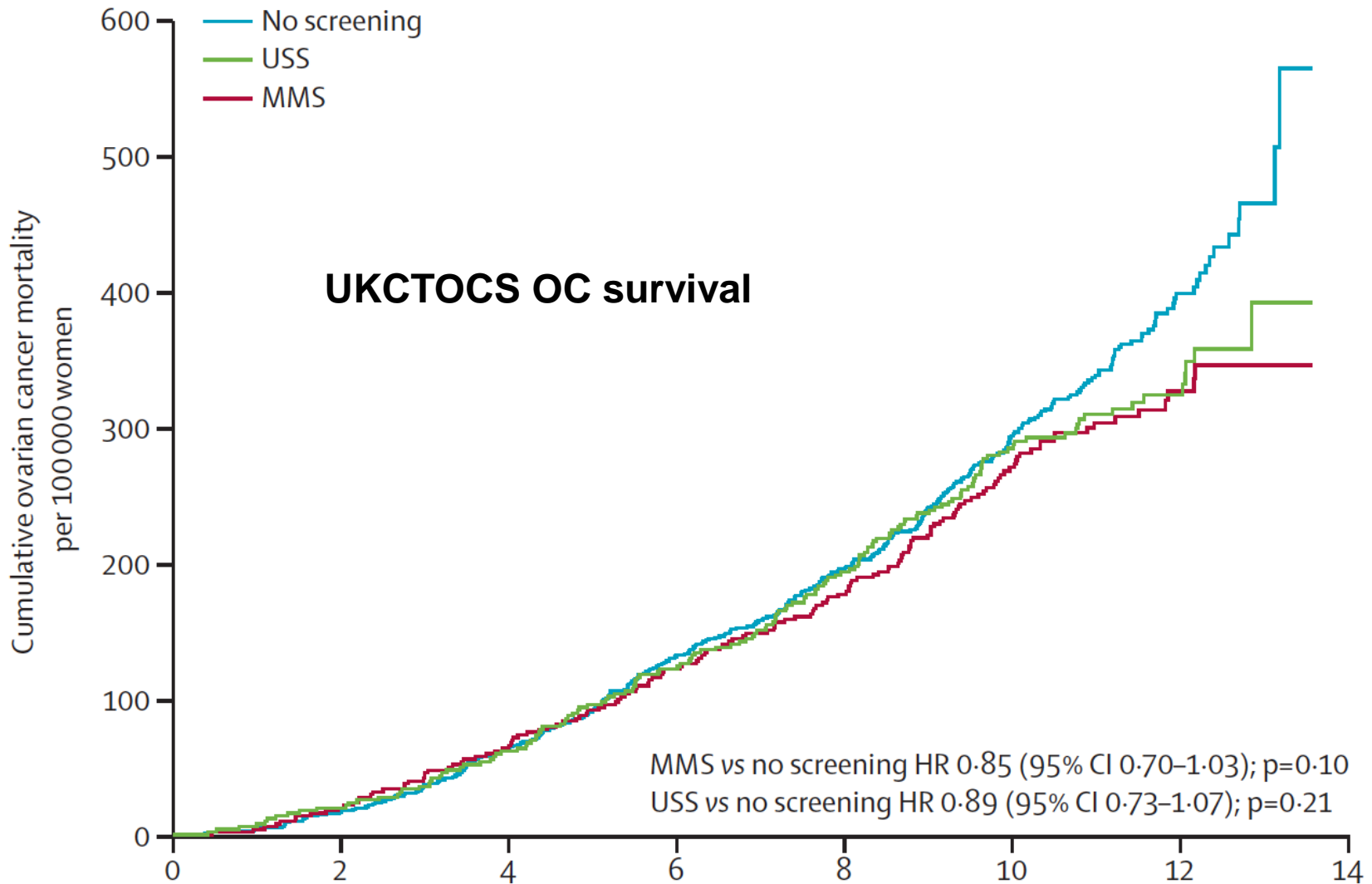
**Pinsky et al, *Int J cancer* 2013
Drescher et al, *J Clin Oncol* 2013**

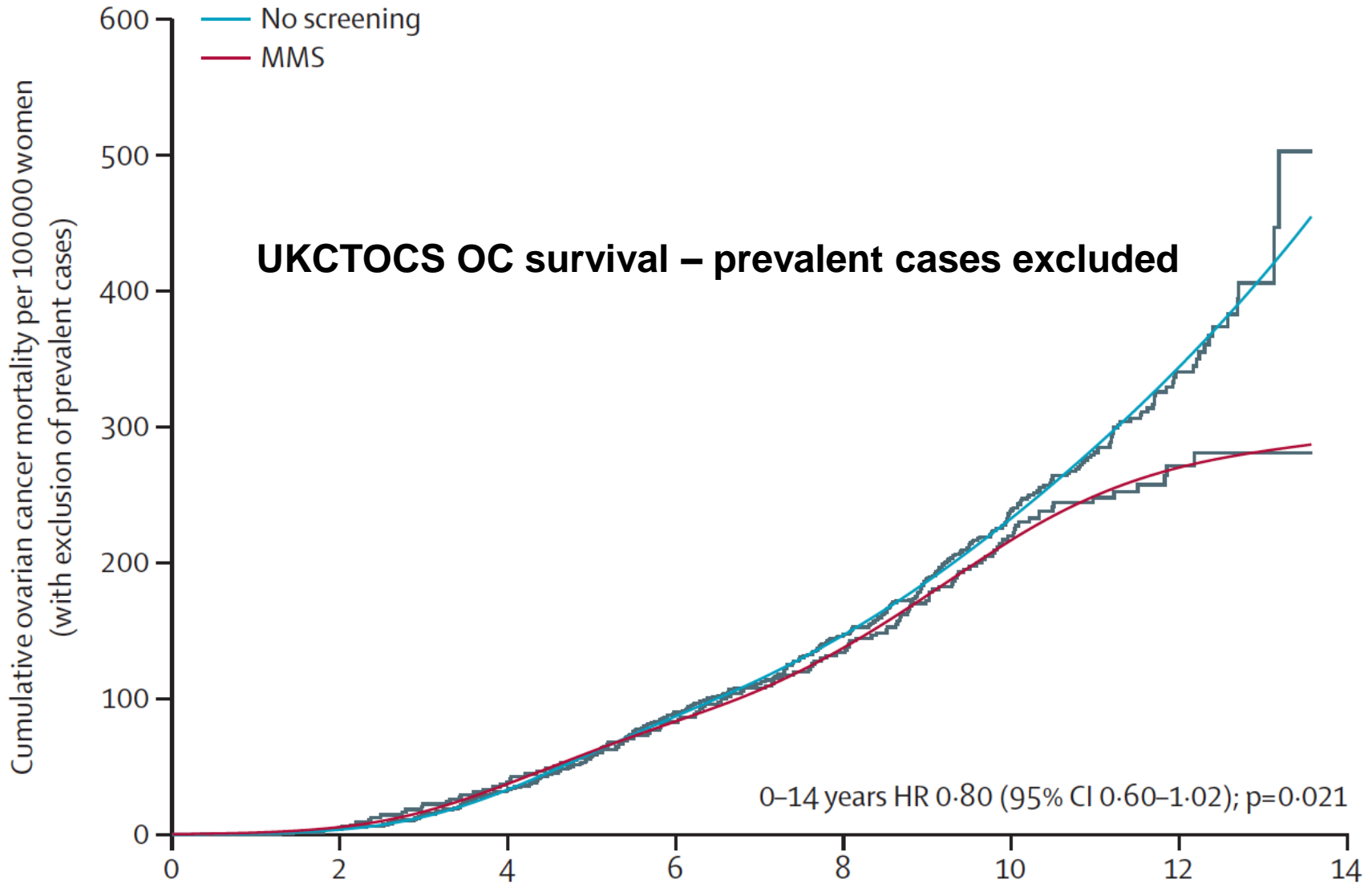
The ROCA Paradigm Shift

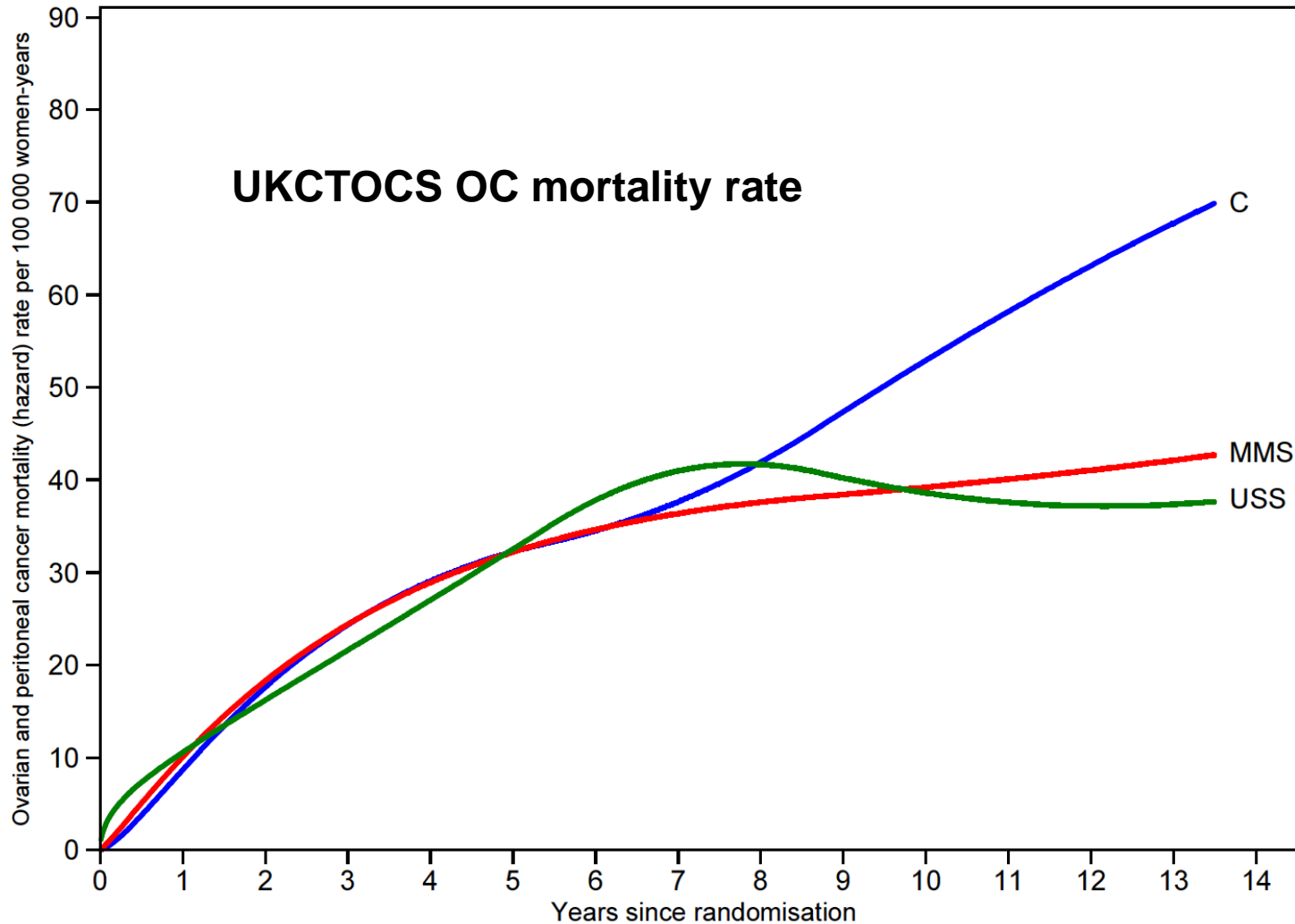
70/133 (53%) screen-detected cancers had CA125 <35u/ml at detection

29/70 (41%) screen-detected cancers where CA125<35u/ml had normal TVS

Rising CA125 levels are suggestive of cancer even when within 'normal range' and even when scan is normal







	Number of women (n)	Deaths (n)	Mortality reduction 0-14 years (%)	p value	Mortality reduction 0-7 years (%)	Mortality reduction 7-14 years (%)
Ovarian cancer (primary analysis)						
Cox model						
MMS	50 624	148	15% (-3 to 30)	0.10
USS	50 623	154	11% (-7 to 27)	0.21
No screening	101 299	347
Royston-Parmar model						
MMS	50 624	148	16% (-1 to 33)	0.11	8% (-20 to 31)	23% (1 to 46)
USS	50 623	154	12% (-6 to 29)	0.18	2% (-27 to 26)	21% (-2 to 42)
No screening	101 299	347
Royston-Parmar model (excluding prevalent cases)						
MMS	50 561	120	20% (-2 to 40)	0.021	8% (-27 to 43)	28% (-3 to 49)
No screening	101 183	281
Weighted log-rank (post-hoc)						
MMS	50 624	148	22% (3 to 38)*	0.023
USS	50 623	154	20% (0 to 35)*	0.049
No screening	101 299	347

Complications in ROCA screening (UKCTOCS)

Complication rate in screen-positive women:

Minor 1.8% (LRTI, wound infection, D+V, uterine perf + UTI + retention)

Major 2.7% (bowel obstruction or injury, CPR, ileus, dehiscence, bleed)

Overall 4.5%

Population screening conclusions (1)

- **Ultrasound lacks specificity as first line test**
- **Multimodal screening with ROCA (1st line) and TVS (2nd line) has acceptable overall sensitivity/specificity and is superior to CA125 with cut-off**
- **Some evidence of increased detection of early stage disease**
- **One small randomised study shows multimodal screening (even with cut-off) improved survival**

Population screening conclusions (2)

- One large RCT (PLCO) shows no mortality benefit (CA125 cut-off, not ROCA)
- Only other large RCT (UKCTOCS) shows probable mortality benefit of ~ 25% using multimodal ROCA-based screening
- If confirmed this is biggest improvement in OC survival since platinum chemo in 1970s
- Evidence of false-positive results leading to surgery / complications
- Women considering screening must be informed of the above

The Future

- **UKCTOCS extended survival analysis 2018**
- **?NHS screening program**
- **novel markers**
- **multiple marker algorithms**
- **use of HE4 and/or contrast enhanced TVS to improve specificity in screen-positive women**

Ovarian Cancer Screening Trials

- Why screen?
- General population screening
- **Rational use of screening in 2016**

Rational use of screening in 2016 (Pre-UKCTOCS final survival analysis results)

General population - postmenopausal >50 yr

- Counsel not yet definite mortality benefit so currently not available on NHS
- In private sector, do not use vaginal examination/TVS or CA125 with cut-off as first line test
- Use annual multimodal approach with ROCA

High risk population – known gene +ve/strong family history >35 yr

- Risk-reducing salpingo-oophorectomy remains standard of care
- Use concurrent ROCA (4-monthly) and TVS (annual) until ready for RRSO (UKFOCSS protocol)
- Do NOT allow screening to delay surgery indefinitely

420,000 OC screening volunteers

Thank You

